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Promising novel treatment against Alzheimer Disease

Research published in *Nature Communications* by **Dr. Andréa LeBlanc** reveals that a Caspase-1 inhibitor that has already proven to be non-toxic for humans in a clinical setting reverses memory deficits and stops Alzheimer disease pathology (AD) in an animal model.

Dr. LeBlanc's team discovered that the Caspase-6 enzyme is highly activated in AD brain lesions and associated with loss of memory. She has pursued the hypothesis that stopping Caspase-6 might provide relief from memory loss and stop progressive dementia. Since there are no specific Caspase-6 inhibitors, they moved upstream, ultimately discovering that Caspase-1 was responsible for activating Caspase-6.

"This was a significant revelation because Caspase-1 inhibitors had been developed for treating inflammatory diseases," explains Dr. LeBlanc. "Thus, we decided to test the effects of a particular Caspase-1 inhibitor, called VX-765, against memory loss and brain pathologies in a mouse model of Alzheimer disease."

VX-765 has an unprecedented beneficial effect in Alzheimer mice. The drug rapidly reverses memory loss, eliminates inflammation, and stops Alzheimer's prototypical amyloid peptide accumulation in the mice brains. In addition to being safe for humans at relatively high doses for extended periods of time, it is capable of reaching the brain, a significant challenge in the development of drugs against disorders of the brain.

While Dr. LeBlanc cautions that there is a considerable bridge to cross between the mouse brain and that of a human, she believes that since her work has first identified the Caspase-1/Caspase-6 neurodegenerative pathway in human neurons and in human Alzheimer brains, there is a chance that this drug will work just as well in humans as it did in mice. Nevertheless, a clinical trial is needed to determine whether the drug will be beneficial against Alzheimer disease in humans.

Samy Suissa elected to Royal Society of Canada

Dr. Samy Suissa, Director of the Centre of Clinical Epidemiology, has been elected to the Royal Society of Canada, Canada's national academy of distinguished scholars, artists, and scientists. Fellows are selected by their peers for outstanding contributions to the natural and social sciences, arts, and humanities.

Dr. Suissa is an internationally renowned pharmacoepidemiologist who studies the real-world safety of medications. His landmark studies on the effects of asthma medications profoundly altered asthma management and contributed to reducing asthma mortality world-wide. His work on the risks of oral contraceptives and hormone therapy in women, and of medications used by the elderly, led to safer clinical practices. He leads the Canadian Network for Observational Drug Effect Studies (CNODES).

SPIN launches online platform to provide self-management tools

At the National Scleroderma Conference, **Dr. Brett Thombs**, founder and director of the Scleroderma Patient-centered Intervention Network (SPIN), announced the launch of the online platform for publically sharing SPIN's upcoming support programs for individuals with this rare autoimmune disease.

Dr. Thombs previewed SPIN's first online patient program, which addresses hand function limitations, to be released in Spring 2019. Jointly developed by patients and rehabilitation specialists, it includes instructional videos for hand exercises, advice for developing a personalized exercise routine, goal-setting and tracking features, and patient stories of their experiences with hand disability and exercises. Once tested, all SPIN programs will be available free-of-charge online, with links provided on the websites of Scleroderma Canada, provincial, and international patient organizations. SPIN has received a generous donation from the JGH Foundation towards dissemination of its programs.

Scleroderma is characterized by hardening of connective tissues, which can substantially damage the skin, blood vessels, muscles, and internal organs. Common problems include limitations in hand function, pain, fatigue, and emotional distress from disfigurement. SPIN was launched in 2011 to connect healthcare professionals and researchers with scleroderma patients, to help them live better with their disease, and to serve as a model framework for other rare diseases.

"People with rare diseases face unique challenges, including a lack of patient-oriented disease management programs to meet their specific needs," said Dr. Thombs "One reason for this is that the small number of patients with any given rare disease is a barrier to effectively developing, testing, and disseminating such programs. To overcome this barrier, SPIN has amassed a large Internet-based cohort of patients, recruited from over 50 treatment centres around the world."

SPIN is finalizing the development and testing of several other self-management programs, which address areas like fatigue, emotional coping, body image concerns, pain, and physical activity. Also in progress are two programs to support scleroderma caregivers and patient leaders of scleroderma support groups.

Inhibitor of stem cell proliferation may have therapeutic potential in cancer

In a paper published in *Developmental Cell,* **Dr. Stéphane Richard**, and his team identified a protein arginine methyltransferase called PRMT5 as a regulator of growth signals emanating from platelet derived growth factor receptor alpha (PDGFRα). The implication of this discovery is that inhibitors of PRMT5 can be used therapeutically to attenuate growth of PDGFRα-addicted cancer cells such as glioblastoma and gastro-intestinal stromal tumors (GIST).

PDGFRα instructs the oligodendrocyte precursor cells (OPC) to proliferate and grow. During myelination, PDGFRα signals diminish, providing the cue for OPCs to become myelinating oligodendrocytes. Dr. Sara Calabretta, a post-doctoral fellow in the Richard lab and the paper's first author, showed for the first time that genetically engineered mice display defects in diminishing PDGFRα signaling in OPCs, which results in mice that lack myelin. This work provides key observations about the process by which myelin in the central nervous system is produced and about the newly discovered relationship between PRMT5 and PDGFRα signaling.

PRMT5 is an interesting enzyme from a therapeutic point of view, as it is overexpressed in many cancers and specific inhibitors have been developed that neutralize its activity. Inhibitors of PRMT5 are currently undergoing clinical trials in patients with mantle cell lymphoma and holds promise for other cancers, including glioblastoma and GIST. By dampening PRMT5 activity, the growth of cells dependent on PDGFRα signaling would be particularly vulnerable.

Prepared by the Research Communications Office,
Lady Davis Institute at the Jewish General Hospital.
Any suggestions with respect to content are welcome.

To submit information or for media enquiries, contact:
Tod Hoffman at: tod.hoffman@ladydavis.ca ;
514-340-8222, ext. 28661

Key components of fracture risk in osteoporosis revealed

Dr. Brent Richards was a senior investigator on the largest study ever to investigate the genetics of osteoporosis and fracture risk. It determined that only two examined factors – bone mineral density (BMD) and muscle strength – play a potentially causal role in the risk of suffering osteoporotic fracture, a major health problem affecting more than 9 million people worldwide very year. Other clinical risk factors like vitamin D levels and calcium intake, historically considered to be crucial mediators of fracture, were not found to directly predispose people in the general population to fracture. This research was published in *The BMJ*.

"These findings suggest that interventions aimed at increasing bone strength are more likely to prevent fractures than widespread supplementation with vitamin D," said Dr. Richards. "Our study, the first genome-wide association study for fracture risk, has provided important insight on the biologic mechanisms leading to fracture and how to prevent it."

The research confirms that BMD is the most important determinant of fracture risk and that prevention strategies aimed at increasing or maintaining bone density are the most likely to be successful. One of the most important aspects of this research is the robust evidence showing that vitamin D supplementation in the general population is unlikely to be effective for the prevention of fracture. This will encourage clinicians to focus patients on building bone density as a more effective preventive measure against fracture. The researchers came to these conclusions by demonstrating that the genetic factors that lead to lowered vitamin D levels in the general population do not increase risk of fracture.

Approximately 30% of people over the age of sixty-five take Vitamin D supplements partly because clinical guidelines for osteoporosis management and fracture prevention suggest such supplements. However, recent large randomized controlled clinical trials have failed to confirm any benefit of vitamin D supplementation in patients without pronounced deficiency of these factors. Thus, these findings and those derived from this study highlight the need to re-assess its widespread use in clinical practice. Researchers do caution that patients using osteoporosis medication should not discontinue their supplements before consulting with their treating physicians.

Certain blood pressure drugs linked to increased risk of lung cancer

The use of angiotensin converting enzyme inhibitors (ACEI) to lower blood pressure is associated with an increased risk of lung cancer compared with the use of another group of blood pressure drugs called angiotensin receptor blockers (ARB), according to a study led by **Dr. Laurent Azoulay** and published in *The BMJ*.

The risk is particularly elevated among people using ACEIs for more than five years, the study found. Although the risk for individual patients is modest, ACEIs are widely prescribed, so these small relative effects could translate into large absolute numbers of patients at risk for lung cancer, say the researchers.

ACEIs are effective drugs used to treat high blood pressure (hypertension). Evidence suggests that ACEIs may increase the risk of lung cancer through the build-up of protein-like chemicals called bradykinin and substance P in the lung. These chemicals have been found on lung cancer tissue, and bradykinin may directly stimulate the growth of lung cancer. However, previous observational studies examining this association are limited and report inconsistent results.

After taking account of potentially influential factors, including age, sex, weight (BMI), smoking status, alcohol related disorders, and history of lung diseases, use of ACEIs was associated with an overall 14% increased risk of lung cancer compared with ARBs. Associations were evident after five years of use and increased with longer durations of use, particularly in patients who used ACEIs for more than 10 years (31% increased risk).

Although the magnitudes of the observed estimates are modest, the researchers point out that ACEIs are one of the most widely prescribed drug classes, so small relative effects could translate into large absolute numbers of patients at risk.

"This is an observational study, so no firm conclusions can be drawn about cause and effect," points out Dr. Azoulay, "and we cannot rule out the possibility that other unmeasured factors, such as socioeconomic differences, diet, and family history of lung cancer, may have affected the results."

The BMJ published a linked editorial.

JGH Department of Dentistry pursues active research programs

There is much to be learned about health in general from what can be discovered through dental research. The Jewish General Hospital (JGH) is one of the few hospitals in Canada where the Department of Dentistry maintains its own active clinical research program.

Largest salivary biobank in Canada

The JGH is home to the largest salivary biobank in all of Canada, with more than 2,500 patients. Under the director-ship of Drs. **Mervyn Gornitsky** and **Hyman Schipper**, the saliva is used to detect biomarkers for cancer, Alzheimer's and Parkinson's diseases, diabetes, chronic pain, scleroderma and temporomandibular disorders (TMD). The department recently completed a large CIHR funded multi-site study with **Dr. Murray Baron** on oral manifestations of scleroderma and the effect on quality of life.

"Saliva would serve as an excellent repository for biomarkers because it is easier to collect than blood or urine and it can be obtained as frequently as necessary," explained Dr. Gornitsky, the Department's Research Director and Chief Emeritus, who has celebrated more than sixty years at the JGH.

Chronic pain and the opioid crisis

Understanding how pain evolves from acute to chronic, and determining who may be susceptible to this transition, may provide clues to help relieve it. Two of **Dr. Ana Velly's** projects involve assessing the risk factors between opioids and cancer: one looks at cancer incidence, the other at cancer recurrence. Both of these projects have received CIHR operating grants, in addition to a third CHIR-funded randomized clinical trial study examining pain management following arthroscopic shoulder surgery that is set to begin this year.

TMD, second only to back disorders as a source of chronic pain, is a particularly troubling condition. Two current projects focus on this problem. One seeks to assess the causes, evaluate underlying risk factors, and to detect salivary biomarkers observable in TMD patients. The other looks at risk factors associated with patients' adherence to treatment.

Early detection of Parkinson's disease

Dr. Schipper examines saliva for biomarkers of oxidative stress, which can be indicative of Parkinson's and Alzheimer's diseases.

"We have observed changes in the tau protein and the enzyme heme oxygenase 1 (HO1) in the saliva of patients with neurodegenerative disease," he said. "Evidence suggests that we may be successful in using saliva to diagnose very early onset. Early diagnosis will enable us to tailor care to suit our patients' needs, possibly delay disease progression, and contribute to higher quality of life for a longer period of time."

Psychosocial care for cancer patients in low income countries

Dr. Melissa Henry co-chaired the International Psycho-social Oncology Society's (IPOS) Research Training Academy to empower the future generation of psycho-oncology researchers from low and middle income countries. These countries, according to the World Health Organization, account for approximately 70% of cancer deaths. The Research Training Academy is an intensive three-day gathering intended to improve global psychosocial care for cancer patients and their loved ones.

"Participants come from all over the world to learn best practices for designing and implementing research projects that will provide evidence-based approaches to psychosocial care," said Dr. Henry. "We are doing more than – hopefully – curing a disease. We are caring for a person who is experiencing a potentially life threatening illness, side effects from treatments, and the emotional impact of confronting morality, physical limitations, and everything else associated with cancer."

The Segal Cancer Centre emphasizes the principle of *whole person care*, which combines treating the physical effects of disease with providing psychosocial support for patients diagnosed with cancer and their caregivers. In many lower income countries health care resources are over-burdened, forcing them to emphasize physical care, while sometimes neglecting psychological and emotional factors. Dr. Henry is on a mission to change this and have patients everywhere receive the psychological and emotional support that is so critical to their well-being and quality of life.

Last year, the Training Academy was held in Kigali, Rwanda and resulted in meetings with the Minister of Health and key officials, who committed to including psycho-oncology as part of their National Cancer Plan. Dr. Henry and other IPOS members drew up a blueprint for implementation.

"The outcome of our Rwandan experience was extremely positive," she reports. "It demonstrated recognition of the importance of psychosocial oncology. Furthermore, it affirmed IPOS as a leader in providing training and mentorship to build the necessary capacity to foster structured clinical and research programs that will improve the patient experience."

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